

Src3: steroid receptor coactivator

10/751113

Δ3-AIB1 = a transcriptional coactivator

• functional studies show ↑ effective coactivator of estrogen, prog + EGF signaling
Attorney Docket No. 54458-20001.00

• isoforms are trans. coactivators of nuclear receptors (eg. estrogen, prog receptors)

Claims:

Src3

1. An isolated protein isoform of an AIB1 transcriptional coactivator.
2. The isoform of claim 1, which is a stronger transcriptional coactivator as compared to wild-type AIB1.

3. The isoform of claim 1, wherein transcriptional coactivation is measured by an in vitro transfection assay.

4. The isoform of claim 1, which coactivates transcription induced by a nuclear receptor.

5. The isoform of claim 4, wherein the nuclear receptor is a bile acid receptors, peroxisome proliferator receptor, a retinoid receptor, a steroid receptor, a thyroid receptor, or a vitamin D receptor.

6. The isoform of claim 5, wherein the steroid receptor is an estrogen receptor or a progesterone receptor.

7. The isoform of claim 1, which coactivates transcription by binding to and enhancing activity of a transcription factor.

8. The isoform of claim 7, wherein the transcription factor is TEF.

9. The isoform of claim 1, which coactivates signaling of a growth factor.

10. The isoform of claim 9, wherein the growth factor is EGF or FGF.

11. The isoform of claim 1, which is over expressed in a cancerous tissue.

12. The isoform of claim 1, which is under expressed in a cancerous tissue.

13. The isoform of claim 11, wherein the cancerous tissue comprises breast tissue, gastrointestinal tissue, head and neck tissue, metastatic tissue, neuroblastoma tissue, ovarian tissue, pancreatic tissue, prostate tissue, stomach tissue, cell-type specific tumors, or combinations thereof.

14. The isoform of claim 1, which contains a deletion.

15. The isoform of claim 14, wherein the deletion comprises all or significant portions of exon 3.

16. The isoform of claim 14, wherein the deletion comprises a binding domain.

• and/or potential growth factor activities

• Trans coactivators functioning by binding to a TF

• can be an estrogen receptor = TF

→ could be a TF or GF

→ could be estrogen

→ could be estrogen

OLD New
1 1 PP

7 2 DNA

8 3 KITSAB NA

9 4 detect PP NA

10 5 detect NA

11 6 Si RAA

12 7 treat use 1

13 8 animal w/ gene

14 9

Ask about sending another

va-54056

GF = EGF, FGF

can bind to estrogen receptor

species election

17. The isoform of claim 16, wherein the binding domain is selected from the group consisting of the domains bHLH, PAS A, PAS B, RID, CID and the exons of wild-type AIB1, and portions and combinations thereof.
18. An isolated nucleic sequences that encodes the isoform of claim 1.
19. The nucleic acid of claim 18, wherein the isoform is ? 3-AIB1.
20. A vector that contains the nucleic acid of claim 18.
21. A recombinant cell that contains the nucleic acid of claim 18.
22. A diagnostic kit for the detection of cancer comprising chemical substances that are specifically reactive to the isoform of claim 1.
23. The diagnostic kit of claim 22, wherein the chemical substances are antibodies or antibody fragments.
24. A diagnostic kit for the detection of cancer comprising chemical substances that are specifically reactive to the nucleic acid of claim 18.
25. The diagnostic kit of claim 24, wherein the chemical substances are nucleic acids that are complementary to said nucleic acid.
26. An antibody or antibody fragment that is specifically reactive to the isoform of claim 1.
27. The antibody or antibody fragment of claim 26, which is an IgG.
28. A nucleic acid that hybridizes under stringent hybridization conditions to the nucleic acid of claim 18.
29. A method for the detection of cancer in a patient comprising:
contacting a biological sample obtained from said patient with one or more chemical substances that specifically bind to the isoform of claim 1; and
detecting binding.
30. The method of claim 29 further comprising comparing the relative amount of isoform in said sample with the amount of wild-type AIB1 protein in said sample to determine a stage of the cancer.
31. A method for the detection of cancer in a patient comprising:

contacting a biological sample obtained from said patient with one or more chemical substances that specifically bind to the nucleic acid of claim 18; and

detecting binding.

32. The method of claim 31 further comprising comparing the relative amount of isoform in said sample with the amount of wild-type AIB1 mRNA in said sample to determine a stage of the cancer.

33. The method of claim 32 wherein the stage comprises a hormone-independent phenotype.

34. A pharmaceutical composition comprising an agent that specifically binds to the isoform of claim 1 and prevents a coactivation of a transcription factor when administered to a patient.

35. The pharmaceutical composition of claim 34, further comprising a pharmaceutically acceptable carrier.

36. An siRNA that inhibits expression of a transcriptional coactivator protein.

37. The siRNA of claim 36, wherein the coactivator protein is selected from the group consisting of Src-1, Src-2, Src-3, and isoforms, fragments and combinations thereof.

38. The siRNA of claim 36, wherein the isoform is β 3-AIB1.

39. The siRNA of claim 36, which binds to a mRNA that encodes β 3-AIB1.

40. The siRNA of claim 36, which comprises sequences from each side of a binding domain of AIB1.

41. The siRNA of claim 40, wherein the binding domain is selected from the group consisting of the domains bHLH, PAS A, PAS B, RID, CID and combinations thereof.

42. The siRNA of claim 36, which comprises nucleic acid strands from about 5 to about 16 nucleotides in length.

43. A pharmaceutical composition comprising:
the siRNA of claim 36; and
a pharmaceutically acceptable carrier.

44. The composition of claim 43 wherein the pharmaceutically acceptable carrier is selected from the group consisting of alcohols, buffers, fatty acids, glycerol, oils, polysaccharides, saccharides, salts, sugars, water, and combinations thereof.

45. The composition of claim 43, further comprising an anti-neoplastic agent effective in the treatment of cancer.

46. The composition of claim 45, wherein the anti-neoplastic agent is selected from the group consisting of agents that inhibit cell growth, agents that inhibit cell proliferation, agents that inhibit cellular differentiation, anti-angiogenic agents, antibodies, antibody fragments, anti-sense agents, chemical agents, cytokines, toxins, and combinations thereof.

47. A method for treating or preventing a tumor comprising administering to a patient a therapeutically effective dose of the pharmaceutical composition of claim 43.

48. The method of claim 47, wherein administration is by direct injection to the tumor.

49. The method of claim 47, further comprising administering additional tumorigenic therapy to said patient.

50. The method of claim 49, wherein the additional tumorigenic therapy is selected from the group consisting of drug therapy, radiation therapy, surgery, and combinations thereof.

51. A transgenic animal comprising a recombinant gene that encodes the isoform of claim 1.

52. The animal of claim 51, which is a mouse.

53. A method for creating the transgenic animal of claim 51.

PHONE CALLS "WHILE OUT" RECORD		PHONE CALL	
TO _____	DATE <u>1/10/66</u>	TIME _____	MESSAGE <u>10/751113</u>
M. _____	OF _____	AREA CODE _____	NUMBER _____
EXTENSION _____		TAKEN BY: _____	
TELEPHONED _____		PLEASE CALL _____	
CALLED TO SEE YOU _____		RETURNED CALL _____	
WILL CALL AGAIN _____		URGENT _____	